

Acute renal failure in patients with chronic kidney disease

Acute renal failure is a (usually) reversible decline in glomerular filtration rate over hours or days.

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Dr Madala's major area of interest is preservation of renal function and prevention of end-stage renal disease.

Acute renal failure (ARF) refers to sudden rapid decline (over hours to days) of glomerular filtration rate (GFR) that is usually reversible.¹ The term 'acute-on-chronic renal failure' has been used when ARF occurs in the background of pre-existing chronic kidney disease. The term 'acute-on-chronic kidney disease' will be used in this review since chronic kidney disease (CKD) has largely replaced 'chronic renal failure' according to the National Kidney Foundation's Kidney/Dialysis Outcomes Quality Initiative guidelines.²

It is important to note that for assessment of renal function, measuring the urea and serum creatinine is inadequate since normal levels do not exclude renal disease. The GFR must be determined and the simplest method for estimating the GFR is through the use of GFR prediction equations that require the age, sex and ethnicity of the individual, as well as the serum creatinine.

Epidemiology

Epidemiological data on acute-on-chronic kidney disease (acute-on-chronic) are limited, as this entity has not been extensively investigated. However, there is clear evidence that pre-existing CKD is a strong risk factor for development of ARF, thus acute-on-chronic forms a significant proportion of ARF. The risk of ARF increases with worsening baseline renal function, with a 3-fold greater risk of ARF when creatinine clearance is < 60 ml/min compared with normal creatinine clearance, while the risk of about 4.5 times has been reported in patients with creatinine clearance below 40 ml/min.³ The incidence of acute-on-chronic varies from 10% to over 30%, depending on the study population. In one of the few community-based studies, acute-on-chronic was reported in almost 13% of patients presenting with ARF.⁴ In contrast, the incidence is higher in hospital-based studies, with acute-on-chronic reported in 30% of ARF occurring in the USA, while the incidence was 33% in Australia and 35.5% in China.⁵⁻⁷

Potentially reversible factors in CKD

Most of the recognised causes of ARF can cause acute-on-chronic and they are traditionally classified into prerenal, intrinsic renal and postrenal causes. This review focuses on the commonly encountered reversible causes that must be considered in patients with CKD who present with unexpectedly rapid deterioration of renal function.

Prerenal causes

In normal kidneys, renal blood flow and GFR remain remarkably constant despite wide variations in blood pressure. This is due

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to renal autoregulation, which determines the balance between vasodilatation of pre-glomerular or afferent arterioles, mediated by renal prostaglandins as well as nitric oxide and vasoconstriction of efferent or post-glomerular arterioles mediated by angiotensin II and endothelin, thus maintaining glomerular filtration pressure. Prerenal failure occurs when renal perfusion becomes diminished beyond the renal autoregulatory capacity. Pre-existing CKD is a major risk factor for prerenal failure and the mechanisms involved are briefly highlighted below.

Extracellular fluid volume depletion

The ability of diseased kidneys to respond to extracellular fluid volume depletion is impaired because of their inability to concentrate the urine, which is lost early in the course of CKD. Extrarenal causes of volume depletion include haemorrhage, diarrhoea and vomiting, etc. Excessive diuresis resulting in volume depletion may occur in patients with CKD, especially with synergistic effects from concurrent use of different diuretic classes.⁸ Osmotic diuresis from concurrent poorly controlled diabetes is another cause. Although fluid restriction is not a usual cause of ARF, CKD patients may develop severe dehydration in the pre-operative period if fluids are restricted prior to surgery, resulting in acute-on-chronic. Therefore, fluid restriction must ensure that renal and extrarenal losses are replaced.

Decreased effective circulating blood volume

Co-morbid illnesses in CKD patients may include congestive cardiac failure, cardio-genic shock, nephrotic syndrome and hepatic cirrhosis. Renal haemodynamic changes resulting from these diseases are similar to those observed with volume depletion, and central venous pressure monitoring is necessary to guide fluid management in the presence of these concomitant disorders to prevent acute-on-chronic. Sepsis as well as septic shock presents another important and common cause of acute-on-chronic.

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Drug-induced haemodynamic renal failure

Altered renal haemodynamics resulting in prerenal failure is a common form of nephrotoxicity that CKD patients are at risk for.

- **Non-steroidal anti-inflammatory drugs.**

All non-steroidal anti-inflammatory drugs (NSAIDs) may induce ARF in patients with CKD since maintenance of renal perfusion is often prostaglandin-dependent. A recent review of the literature on the renal effects of NSAIDs showed that selective COX-2 inhibitors, like the non-selective NSAIDs, cause ARF in patients with CKD and must be used cautiously or avoided in these patients.⁹ Acute-on-chronic secondary to NSAID use may present with prerenal failure, acute tubular necrosis or acute interstitial nephritis.

- **Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.**

Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) may precipitate acute-on-chronic in patients with bilateral renal artery stenosis since GFR in such patients is dependent on angiotensin II-mediated efferent arteriolar vasoconstriction. ACE-Is and ARBs reduce the synthesis as well as effect of angiotensin II, respectively, resulting in loss of the compensatory efferent arteriolar vasoconstriction; this precipitates a fall in GFR and worsening of renal function within 72 hours of starting treatment. However, renal function rapidly returns to baseline after drug withdrawal.^{10,11} Unlike NSAIDs, ACE-Is and ARBs do not usually cause acute tubular necrosis (ATN).

- **Radiocontrast agents.**

Iodinated contrast media have long been established as a cause of ARF and there is widespread evidence that the risk for contrast-induced nephrotoxicity is greatest in CKD patients with GFR below 60 ml/min.¹² Gadolinium, used in magnetic resonance imaging, is also increasingly being recognised as nephrotoxic and a cause of acute-on-chronic in patients with moderate as well as severe CKD.¹³ The incidence of acute-on-chronic secondary to contrast-induced nephrotoxicity increases as the baseline serum creatinine increases, ranging from 2% if baseline serum creatinine is $\leq 105 \mu\text{mol/l}$ while increasing up to

62% if baseline serum creatinine is $\geq 180 \mu\text{mol/l}$.¹⁴ The mechanism of contrast-induced nephrotoxicity is complex and poorly understood but it appears to be mediated through hypoxic tubular damage in the renal medulla due to alterations in the renal microcirculation as well as through increased oxygen consumption for solute reabsorption. Structural as well as functional abnormalities of CKD such as defective nitric-oxide-dependent vasodilatation, impaired renal prostaglandins synthesis and increased reabsorptive workload by surviving nephrons thus render the diseased kidneys susceptible to contrast-induced injury.

Intrinsic causes

Acute tubular necrosis

Patients with CKD are at risk for ATN, which occurs as a result of ischaemia or exposure to nephrotoxins. Ischaemic ATN is the result of uncorrected prolonged renal hypoperfusion and most of the causes of prerenal failure have the potential to cause ATN. Toxic ATN is due to direct tubular epithelial injury by both endogenous toxins, as is the case with myoglobinuric ARF, myeloma kidney, hypercalcaemia, etc., as well as exogenous nephrotoxins such as aminoglycosides, radiocontrast agents, etc.^{8,15} Acute-on-chronic may also complicate treatment with amphotericin B, which causes both ischaemic and toxic tubular injury.^{15,16}

Acute interstitial nephritis

Acute drug-induced interstitial nephritis is a common cause of intrinsic ARF that can lead to acute-on-chronic in CKD patients. Common precipitants are NSAIDs and penicillins. Infections cause direct damage to the tubulointerstitium resulting in acute pyelonephritis. However, infection-associated acute interstitial nephritis is immunologically mediated.¹⁷

Crystal-induced ARF

Pre-existing CKD is also an important risk factor for the development of crystal-induced ARF. Some of the commonly used drugs associated with crystal-induced ARF include acyclovir, sulphonamides and indinavir.^{8,18} Recognition of these drugs, commonly indicated in immunocompromised patients, as a cause of acute-on-chronic is important as the burden of CKD among patients with

human immunodeficiency virus (HIV) infection is likely to grow because of the expected improved survival of HIV-infected patients following the recent country-wide introduction of highly active antiretroviral treatment.

Severe hypertension

Accelerated phase or malignant hypertension may present with oliguric ARF with recovery of renal function if adequate blood pressure control is achieved.¹⁹ The time period to renal function recovery is variable and has been observed within 10 days, ranging up to 9 months with optimal blood pressure control, as well as dialysis support where indicated. Prognosis for renal recovery is better in patients who have normal kidney size and those with concurrent ATN on renal histology.¹⁹ Acute-on-chronic developing after commencing ACE-I in a hypertensive patient is an indication to search for renal artery stenosis.

Relapse or progression of underlying disease

Rapidly progressive glomerulonephritis must be considered in someone presenting with ARF as well as in previously stable patients known to have glomerulonephritis who develop sudden, rapid unexpected decline in GFR or rising serum creatinine, since early treatment may lead to sufficient renal recovery and may obviate the need for chronic dialysis and transplantation. Acute-on-chronic may be a manifestation of relapse of disease activity in patients with CKD due to lupus nephritis. Flare-up of lupus nephritis accounted for 20% of acute-on-chronic in the previously cited Chinese study.⁴

Postrenal causes

Obstruction of the upper and lower urinary tracts may occur in the setting of pre-existing CKD whether CKD is due to an obstructive or another cause, and should be considered in all patients presenting with acute-on-chronic. Urgent intervention is critical to limit renal damage and preserve residual renal function in these patients. Obstruction can be immediately excluded by non-invasive imaging, i.e. ultrasonography, computed tomography and magnetic resonance imaging. Relief of obstruction often requires early urology referral.

Diagnostic approach and management of acute-on-chronic kidney disease

The approach to diagnosis of any patient presenting acutely with renal failure should mainly address the following two issues:

- Is the renal failure acute or is it acute-on-chronic?
- Identifying and managing potentially reversible causes.

Establishing whether renal failure is acute or acute-on-chronic

- History may indicate the presence of pre-existing renal disease or predisposing factors for CKD, the common risk factors being hypertension, diabetes mellitus, autoimmune disease, chronic analgesic use, etc.
- Clues on clinical examination include proteinuria and/or haematuria on dipstick examination, which may suggest

glomerular disease. Other clues are the presence of extrarenal organ involvement like hypertensive heart disease and/or retinopathy; diabetic micro- and macrovascular complications and extra-renal manifestations of systemic lupus erythematosus.

- Useful investigations include previous results of serum creatinine and, where available, a sudden increase of more than 25 - 50% from baseline serum creatinine usually indicates acute-on-chronic. Ultrasound usually shows shrunken kidneys with the exception of diabetic nephropathy, amyloidosis, HIV-associated nephropathy and autosomal

dominant polycystic kidney disease, in which kidney size usually remains preserved.

Identification and management of acute-on-chronic kidney disease

Table I summarises the clinical approach to the diagnosis as well as the appropriate management of the reversible causes of deteriorating renal function in CKD patients commonly encountered in clinical practice. History and physical examination will often give clues to the likely cause of the acute deterioration. In prerenal causes of acute-on-chronic, evidence of hypovolaemia is easily established through insertion of a central venous catheter and confirmation

Table I. Diagnosis and management of common reversible causes of acute renal failure in patients with CKD

History	Clinical features	Specific investigations	Management
Prerenal causes			
<ul style="list-style-type: none"> • Gastrointestinal loss: diarrhoea, vomiting, etc. • Skin loss: excess sweating, burns • Renal loss: diuretics, osmotic diuresis, etc. • Haemorrhage 	<ul style="list-style-type: none"> • Signs of dehydration: dry oral mucosa, reduced skin turgor, etc. and hypotension • Skin and renal losses may have same features as above • Above and clues to the source of bleeding 	<ul style="list-style-type: none"> • Central venous catheter insertion and monitoring usually show low central venous pressure (CVP) except in congestive cardiac failure/ cardiogenic shock 	<ul style="list-style-type: none"> • Fluid resuscitation and restoration of hypovolaemia
<ul style="list-style-type: none"> • Symptoms of cardiac failure • History may suggest other oedema states 	<ul style="list-style-type: none"> • Signs of congestive cardiac failure/ cardiogenic shock • Signs suggestive of cirrhosis or nephrotic syndrome 		<ul style="list-style-type: none"> • Inotropic drugs may be indicated in congestive cardiac failure/ cardiogenic shock
Intrinsic renal causes			
<ul style="list-style-type: none"> • History of above prerenal causes • History of nephrotoxic or crystal-inducing drug • Pyelonephritis and systemic infection • Autoimmune flares may be suspected from history or from routine serological surveillance tests 	<ul style="list-style-type: none"> • Signs of dehydration, low BP, etc. • Nonspecific signs • Clinical signs of infection • Recurrence or worsening of proteinuria and/or haematuria on urine dipstick testing • Extrarenal features may be present • Severe hypertension, grade III/ IV retinopathy and worsening renal function 	<ul style="list-style-type: none"> • Low CVP as above • No specific tests needed • Microscopy and culture of urine/ blood/ sputum • Specific serological tests, e.g. antinuclear factor, streptococcal antibodies, antineutrophil cytoplasmic antibodies (ANCA), etc. • Renal biopsy • Clinical diagnosis 	<ul style="list-style-type: none"> • Fluid replacement • Withdraw offending drug • Appropriate antibiotic therapy • Nephrology referral for renal biopsy and immunosuppressive therapy is required to reverse acute-on-chronic or prevent further loss • Blood pressure control
Postrenal causes			
<ul style="list-style-type: none"> • Symptoms of urinary retention and/ or prostatism • Symptoms of cystitis (dysuria suprapubic pain, etc.) • Ureteric colic 	<ul style="list-style-type: none"> • Distended, palpable bladder • Prostate enlargement • Variable abdominal tenderness suprapubic, flank 	<ul style="list-style-type: none"> • Ultrasound shows hydronephrosis • Urine microscopy and culture showing infection • Renal calculi on X-ray or ultrasound 	<ul style="list-style-type: none"> • Urology referral and relief of obstruction is required

of a low central venous pressure. Fluid resuscitation and volume replacement will usually be adequate to restore renal function back to its baseline level. However, once ischaemic ATN is established, temporary dialysis may be indicated until renal recovery back to baseline occurs. Inotropic drugs are required to restore renal perfusion and renal function in patients who develop acute-on-chronic as a result of cardiogenic shock.

Similarly, postrenal causes are often evident on history as well as physical examination, and obstruction can be confirmed with non-invasive imaging like ultrasonography, which must be done urgently to facilitate timeous relief of obstruction before permanent renal damage has ensued. Relief of obstruction leads to reversal of renal function deterioration and recovery back to baseline or renal function stabilisation.

Once prerenal and postrenal causes of acute-on-chronic have been excluded clinically and on the simple investigations discussed, an intrinsic renal cause must be sought, which might require special investigations. In drug-induced acute-on-chronic, withdrawal of the offending drug may be all that is required. Systemic infections and pyelonephritis must be treated according to results of microscopy, culture and antimicrobial sensitivity. Accelerated hypertension requires modification of the antihypertensive treatment regimen. It is important to ensure compliance with salt restriction, so a dietician must be consulted to optimise adherence to diet therapy and limit the potential for dietary salt indiscretion as a cause for poor blood pressure control. If there are indications, dialysis may be required for a variable period until baseline renal function is achieved.

Suspected relapse of lupus nephritis as well as rapidly progressive renal disease due to other glomerulonephritides like

the vasculitides must be confirmed with appropriate specific serological tests, i.e. antinuclear antibodies, serum complement, antineutrophil cytoplasmic antibodies, etc. A renal biopsy is required to confirm the diagnosis as well as assess histological activity and disease stage in order to guide further decisions regarding the immunosuppressive therapeutic regimen. Temporary dialysis may be required, where indicated, as discussed with all other causes of acute-on-chronic.

Conclusion

Prevention of ARF is crucial in CKD patients in whom the ultimate goal is preserving renal function and delaying the onset of end-stage renal disease. Once acute-on-chronic has developed it is mandatory to look for the cause and removal of the precipitating factor and/or appropriate treatment will often result in recovery or stabilisation of renal function.

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In a nutshell

- Chronic kidney disease (CKD) patients are at a high risk for acute renal failure.
- Glomerular filtration rate must be estimated in all patients with hypertension, diabetes and other CKD risk factors for diagnosis and staging of CKD.
- Always look for reversible causes in patients presenting with renal failure.
- Correction of hypovolaemia and hypotension restores baseline renal function in prerenal causes.
- Immediate relief of obstruction is critical to prevent further kidney damage in postrenal acute-on-chronic.
- Avoid NSAIDs, nephrotoxic antimicrobials and radiocontrast agents in CKD patients.
- ACE-Is and ARBs must be stopped if serum creatinine increases more than 15% from baseline value within a week of starting treatment.
- Optimal BP control may result in renal recovery in accelerated phase hypertension.
- Urgent referral for renal biopsy is mandatory where recurrence of active lupus nephritis or rapidly progressive glomerulonephritis are suspected.
- Preserving renal function and delaying onset of chronic dialysis is the ultimate goal in the care of CKD patients.